



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<p>(21) International Application Number: PCT/EP99/00852</p> <p>(22) International Filing Date: 5 February 1999 (05.02.99)</p> <p>(30) Priority Data: 98200400.4 9 February 1998 (09.02.98) EP</p> <p>(71) Applicant (for all designated States except US): DUPHAR INTERNATIONAL RESEARCH B.V. [NL/NL]; C.J. Van Houtenlaan 36, NL-1381 CP WEESP (NL).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): DEN HARTOG, Jacobus A., J. [NL/NL]; (NL). VISSER, Gerben, M. [NL/NL]; (NL). VAN STEEN, Bartholomeus, J. [NL/NL]; (NL). TULP, Martinus, T., M. [NL/NL]; (NL). RONKEN, Eric [NL/NL]; (NL). KRUSE, Cornelis, G. [NL/NL]; (NL). LANGE, Josephus H., M. [NL/NL]; Duphar International Research B.V., C.J. Van Houtenlaan 36, NL-1381 CP Weesp (NL).</p> <p>(74) Agent: MUIS, Maarten; c/o Octrooibureau Zoan B.V., C.J. Van Houtenlaan 36, NL-1381 CP Weesp (NL).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published Without international search report and to be republished upon receipt of that report.</p>
<p>(54) Title: BENZISOXAZOLE DERIVATIVES HAVING D4-ANTAGONISTIC ACTIVITY</p> <div style="text-align: center;"> <p>(I)</p> </div> <p>(57) Abstract</p> <p>The present invention relates to a group of novel benzisoxazole derivatives which are potent and selective antagonists of the dopamine D4-receptor. The compounds have general formula (I) wherein (R₁)_n represents 0, 1, or 2 substituents, which can be the same or different, from the group C₁₋₃-alkyl or alkoxy, halogen, trifluoromethyl, nitro, amino mono- or dialkyl (C₁₋₂)-amino, sulfonyl-(C₁₋₃)alkyl or -alkoxy, sulfonyl trifluoromethyl, sulfonyl amino, and sulfonyl mono- or dialkyl (C₁₋₂)-amino, X is O, S, NH or NCH₃, Y represents CH₂ or (CH₂)₂, (R₂)_m represents 0, 1, or 2 substituents, which can be the same or different, from the group methyl and ethyl, or (R₂)_m is a methylene bridge or ethylene bridge, A is a group -CH₂-(CRH)_p- wherein R is hydrogen or methyl and p is 0 or 1, and B represents 2- or 3-indolyl or 2-benzimidazolyl, which groups may be substituted at carbon with 1 or 2 substituents from the group C₁₋₃-alkyl or alkoxy, halogen, trifluoromethyl, nitro, amino, mono- or dialkyl (C₁₋₂)amino, sulfonyl-(C₁₋₃)alkyl or -alkoxy, sulfonyl trifluoromethyl, sulfonyl amino, and sulfonyl mono- or dialkyl (C₁₋₂)-amino.</p>		

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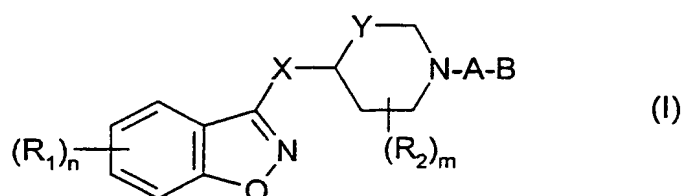
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Benzisoxazole derivatives having D4-antagonistic activity

The present invention relates to a group of novel benzisoxazole derivatives, to a method for the preparation of these compounds, and to
 5 pharmaceutical compositions containing one or more of these compounds as an active component.

It has surprisingly been found that the compounds and salts thereof of the formula (I)

10



wherein

- $(R_1)_n$ represents 0, 1 or 2 substituents, which can be the same or
 15 different, from the group C_{1-3} -alkyl or alkoxy, halogen, trifluoromethyl, nitro, amino, mono- or dialkyl (C_{1-2}) -amino, sulfonyl- (C_{1-3}) alkyl or -alkoxy, sulfonyl trifluoromethyl, sulfonyl amino, and sulfonyl mono- or dialkyl (C_{1-2}) -amino,
- X is O, S, NH or NCH_3 ,
- 20 – Y represents CH_2 or $(CH_2)_2$
- $(R_2)_m$ represents 0, 1, or 2 substituents, which can be the same or different, from the group methyl and ethyl, or $(R_2)_m$ is a methylene bridge or ethylene bridge,
- A is a group $-CH_2-(CRH)_p-$ wherein R is hydrogen or methyl and p is 0 or
 25 1, and
- B represents 2- or 3-indolyl or 2-benzimidazolyl, which groups may be substituted at carbon with 1 or 2 substituents from the group C_{1-3} -alkyl or alkoxy, halogen, trifluoromethyl, nitro, amino, mono- or dialkyl (C_{1-2}) amino, sulfonyl- (C_{1-3}) alkyl or -alkoxy, sulfonyl trifluoromethyl, sulfonyl amino, and sulfonyl mono- or dialkyl (C_{1-2}) -amino,
 30 are potent and selective antagonists of the dopamine D4-receptor.

Compounds having formula (I) wherein A is the group CH₂, Y is CH₂, X is O, NH or NCH₃ and m and n are 0, and B has the above meaning, and salts thereof are preferred.

- 5 Due to the potent and selective D4 antagonistic activity the compounds according to the invention are suitable for use in the treatment of psychiatric disorders such as psychosis, anxiety, depression, attention deficits and memory disorders, neurological disorders such as Parkinson's disease and ischaemia and other CNS-diseases involving dopaminergic
10 neurotransmission.

The affinity of the compounds of the invention for dopamine D4 receptors was determined using CHO-K1 cells which are stably transfected to express the human recombinant dopamine receptor, D4.2 subtype (Van
15 Tol et al, Nature 350, 610, 1991) and using [3H]-Spiperone as the ligand. After incubation of a freshly prepared cellmembrane preparation with the [3H]-ligand, with or without addition of compounds of the invention, separation of bound and free ligand was performed by filtration over glassfiberfilters (Research Biochemicals International protocol, Catalog No.
20 D-177). Radioactivity on the filter was measured by liquid scintillation counting. Results are expressed as IC50 values and transformed into inhibitory constants (Ki).

The dopamine D4 antagonistic activity of compounds of the invention was
25 determined by functional studies using CHO-K1 cells stably expressing the human dopamine D4.4 receptor (Van Tol et al, Nature 358, 149, 1992). These cells were fitted with a construct encoding a truncated form of alkaline phosphatase, causing it to get secreted by the cells. Expression of this secretable alkaline phosphatase (SeAP) is under direct control of
30 cellular cyclic AMP (Berger et al, Gene, 66, 1, 1988). SeAP measurements were done with p-nitrophenylphosphate (pNPP) as the substrate using colorimetric readout at 450 nm. Dopamine D4 antagonist activity was determined by co-incubation of cells with prostaglandin PGE1 (1µM) and quinpirole (1µM), with or without addition of compounds of the invention, for
35 receptor-mediated stimulation of adenylate cyclase and for maximal dopamine D4 receptor-mediated suppression, respectively. The antagonistic effect of compounds of the invention against agonist

dependant attenuation of dopamine D4 receptor mediated SeAP formation was quantified, yielding estimates of intrinsic activity and potency (pA2 values). Clozapine and spiperone were used as reference dopamine antagonists.

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Absence of dopamine D4 agonistic activity was confirmed using the same assay, but leaving out the standard dopamine D4 agonist quinpirole, by determination of the concentration-dependant attenuation of the dopamine D4 receptor mediated SeAP formation by compounds of the invention.

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Dopamine D4 antagonist properties and absence of dopamine D4 agonist properties of selected compounds of the invention were further confirmed using radioactive measurements of cAMP formation according to Salomon et al. (Anal Biochem, 58, 541, 1974) as modified by Weiss et al. (J Neurochem 45, 869, 1985).

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The selectivity of the compounds of the invention with regard to the dopamine D2 receptor, was determined by measuring the affinity for dopamine D2 receptors using rat brain homogenates and [3H]-Spiperone as the ligand (Leysen et al, Biochem Pharmacol 27, 307, 1978). After incubation of a freshly prepared cellmembrane preparation with the [3H]-ligand, with or without addition of compounds of the invention, separation of bound and free ligand was performed by filtration over glassfiberfilters. Radioactivity on the filter was measured by liquid scintillation counting. Results are expressed as IC50 values and transformed into inhibitory constants (Ki).

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The dopamine D2 (ant)agonistic activity of compounds of the invention was determined by functional studies based on radioactive measurements of cAMP formation according to Salomon et al. (Anal Biochem, 58, 541, 1974), as modified by Weiss et al. (J Neurochem, 45, 869, 1985), using CHO cells, stably expressing human dopamine D2L receptors (Grandy et al, Proc Natl Acad Sci USA, 86, 9762, 1989).

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Suitable acids with which the compounds can form pharmaceutically acceptable acid addition salts are for example hydrochloric acid, sulphuric acid, phosphoric acid, nitric acid, and organic acids such as citric acid,

fumaric acid, maleic acid, tartaric acid, acetic acid, benzoic acid, p-toluene sulphonic acid, methane sulphonic acid and naphthalene sulphonic acid.

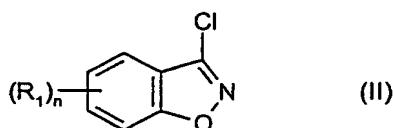
5 The compounds of the invention can be brought into forms suitable for administration by means of usual processes using auxiliary substances and/or liquid or solid carrier materials.

10 The compounds of the invention having formula (I) can be obtained according to methods known for the synthesis of structurally related compounds.

A suitable synthesis for the compounds according to the present invention is the following:

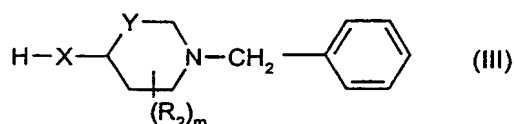
15 Step 1

Reaction of a compound having formula (II)



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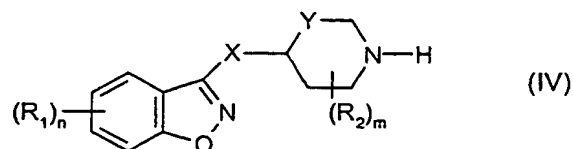
with a compound of the formula (III)



25 This reaction is carried out in a polar aprotic solvent such as dimethylformamide in the presence of an equivalent amount of a base such as sodiumhydride at 20 - 120°C. The protecting benzyl group is then removed from the obtained product.

30 Step 2

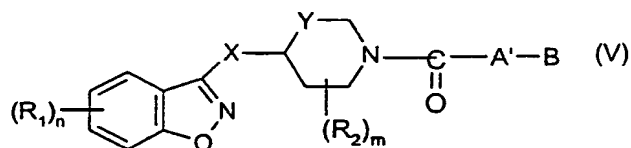
When B is the group 2- or 3-indolyl, the thus obtained deprotected compound having formula (IV)



- is reacted with an optionally substituted 2- or 3-indolyl carboxylic acid derivative of the formula B-A'-COOH, wherein A' is the group -(CRH)_p-, wherein R is hydrogen or methyl and p has the value 0 or 1. This reaction is carried out in the presence of an equivalent amount of 1,1'-carbonyldiimidazole in an aprotic solvent such as tetrahydrofuran.

10 Step 3

The keto group in the obtained compound of the formula (V)



- is reduced to CH₂ in a manner known per se, e.g. by means of an excess of sodium borohydride in the presence of acetic acid in a solvent such as dimethoxyethane under an atmosphere of nitrogen to give the desired compound having formula (I).
- To prepare a compound having formula (I) wherein B is the group 2-benzimidazolyl, the compound having formula (IV) is reacted with an optionally substituted 2-halomethyl benzimidazole derivative of the formula B-A-Z, wherein A has the above meaning and Z is Cl or Br. This reaction is carried out in the presence of a base such as triethylamine in a polar aprotic solvent such as acetonitrile at 20 - 80°C.

The preparation of the compounds is illustrated in the following examples.

Example I

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3-(4-Oxo-[1-(2-methylindolyl)piperidino])-benzisoxazole.hydrochloride

Part A: A quantity of 19.1 g (100 mmol) of commercially available, dry 4-hydroxy-1-benzyl-piperidine was dissolved in dimethylformamide (150 ml) and 6.4 g (55% quality; 100 mmol) sodiumhydride was added. After stirring at 80 °C for 1 hr the mixture was cooled to room temperature and 15.4 g (100 mmol) of 3-chloro-benzisoxazole ((H. Boshagen, Chem. Ber. 1967, 100, pg 3326) was added in portions. After stirring at room temperature for 1 hr and at 80 °C for 3 hr, the mixture was cooled to room temperature and water (300 ml) was added. The solution was extracted with dichloromethane (three times 150 ml), the organic layer was subsequently washed with water (three times 40 ml), dried over magnesium sulphate and concentrated *in vacuo*. The product was purified applying flash-chromatography over silicagel using dichloromethane/methanol 99:1 as the eluent. After concentration *in vacuo* a total of 25.6 g of 3-(4-oxo-1-benzyl-piperidino)-benzisoxazole was obtained (83% yield)

Part B: To a solution of 25.6 g (83 mmol) of 3-(4-oxo-1-benzyl-piperidino)-benzisoxazole in 1,2-dichloroethane (200 ml) a solution of 1-chloroethyl chloroformate (13.6 ml, 125 mmol, 1.5 equivalent) was added dropwise under ice cooling. The mixture was stirred at 0 °C for 1/2 hr, at room temperature for 1 hr, refluxed for 2 hrs and subsequently cooled to room temperature. After concentration *in vacuo* , methanol (200 ml) was added and the resulting mixture was refluxed for 2 hrs. The precipitate obtained after subsequent cooling to 0°C was collected by filtration, washed with petroleum-ether (40-60) and dried *in vacuo*. In this way 14.5 g of 3-(4-oxo-piperidino)-benzisoxazole.hydrochloride was obtained as a pink solid (69 % yield).

Part C: A quantity of 9.7 g (60 mmol) of commercially available indole-2-carboxylic acid and 9.8 g (60 mmol) of commercially available 1,1'-carbonyldiimidazole were dissolved in dry tetrahydrofuran (300 ml) , the reaction mixture was refluxed under nitrogen for 1 hr and subsequently cooled in ice.

Meanwhile the obtained 14.5 g (57 mmol) of 3-(4-oxo-piperidino)-benzisoxazole.hydrochloride was dissolved in a sodium hydroxide solution in water (2N, 200 ml) and extracted with dichloromethane (three times 100 ml). The combined organic layers were dried over sodium sulphate, concentrated *in vacuo* and dissolved in dry tetrahydrofuran (70 ml). The

obtained solution of 3-(4-oxo-piperidino)-benzisoazole was added to the solution of activated indole-2-carboxylic acid and the resulting reaction mixture was refluxed for 2 hrs. After concentration *in vacuo*, water (200 ml) was added. After washing with dichloromethane (three times 70 ml) the combined organic layers were washed with water (three times 40 ml), dried over sodium sulphate and concentrated *in vacuo*. The resulting yellow solid was suspended under stirring in diisopropylether (300 ml). After 40 hrs the precipitate was collected by filtration, washed with diisopropylether (two times 150 ml) and dried *in vacuo*. A quantity of 18.4 g of 3-(4-oxo-[1-(2-carboxy-indolyl)piperidino])benzisoazole was obtained as a white solid (89 % yield).

Part D: To a solution of 18.4 g (50 mmol) of 3-(4-oxo-[1-(2-carboxy-indolyl)piperidino])benzisoazole and 9.5 g (250 mmol, 5 equivalent) of sodium borohydride in dry 1,1-dimethoxyethane (400 ml) under nitrogen, a solution of 14.3 ml (250 mmol) acetic acid in dry 1,2-dimethoxyethane (100 ml) was added dropwise in 1/2 hr. The mixture was refluxed for 1 hr. After cooling of the reaction mixture in ice, subsequent dropwise addition was carried out of: 1). a mixture of water (9.5ml) and 1,2-dimethoxyethane (100ml), 2). water (90ml) and 3). a solution of sodiumhydroxide in water (2N, 15 ml). The reaction mixture was refluxed for 2 hrs. The precipitate obtained after cooling to room temperature was removed by filtration. To the filtrate water (300 ml) and ethylacetate (50 ml) were added, the water layer was further extracted with ethylacetate (two times 150 ml) and the combined organic layers were washed with water (three times 70 ml), dried over sodium sulphate and concentrated *in vacuo*. The residual yellow oil was dissolved in absolute ethanol (200 ml), heated to 70°C and a solution of 1.83 g hydrochloride (50 mmol) in absolute ethanol (15 ml) was added. After stirring for 1/2 hr at 70°C ,subsequent cooling and stirring at room temperature for 2 hrs, the resulting precipitate was collected by filtration, washed with absolute ethanol (two times 25 ml) and dried *in vacuo*. In this way 15.2 g of 3-(4-oxo-[1-(2-methylindolyl)piperidino])-benzisoazole.hydrochloride was obtained as a white solid (79% yield) with a melting point of 225°C.

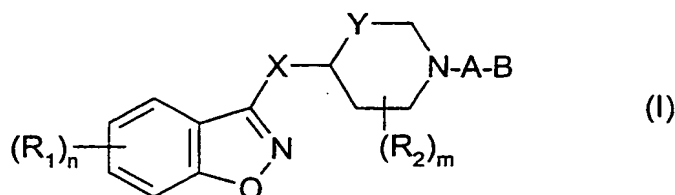
In an analogous manner the compounds having formula (I) listed below have been prepared:

Table

Example	(R ₁) _n	X	Y	(R ₂) _m	A	B	Salt
II	H	NCH ₃	CH ₂	H	CH ₂	2-indolyl	base
III	H	NH	CH ₂	H	CH ₂	2-indolyl	fumarate
IV	H	NCH ₃	CH ₂	H	CH ₂	2-benzimidazolyl	HCl
V	H	NCH ₃	CH ₂	H	CH ₂	4-Cl-2-indolyl	base
VI	H	NCH ₃	CH ₂	H	CH ₂	5-F-2-indolyl	base
VII	H	NCH ₃	CH ₂	H	CH ₂	3-indolyl	fumarate

Claims:

1. A compound of formula (I) or a salt thereof



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wherein

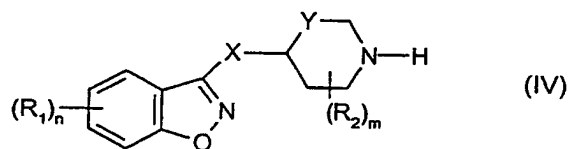
- $(R_1)_n$ represents 0, 1 or 2 substituents, which can be the same or different, from the group C_{1-3} -alkyl or alkoxy, halogen, trifluoromethyl, nitro, amino mono- or dialkyl (C_{1-2}) -amino, sulfonyl- (C_{1-3}) alkyl or -alkoxy, sulfonyl trifluoromethyl, sulfonyl amino, and sulfonyl mono- or dialkyl (C_{1-2}) -amino,
- X is O, S, NH or NCH_3 ,
- Y represents CH_2 or $(CH_2)_2$
- $(R_2)_m$ represents 0, 1, or 2 substituents, which can be the same or different, from the group methyl and ethyl, or $(R_2)_m$ is a methylene bridge or ethylene bridge,
- A is a group $-CH_2-(CRH)_p-$ wherein R is hydrogen or methyl and p is 0 or 1, and
- B represents 2- or 3-indolyl or 2-benzimidazolyl, which groups may be substituted at carbon with 1 or 2 substituents from the group C_{1-3} -alkyl or alkoxy, halogen, trifluoromethyl, nitro, amino, mono- or dialkyl (C_{1-2}) amino, sulfonyl- (C_{1-3}) alkyl or -alkoxy, sulfonyl trifluoromethyl, sulfonyl amino, and sulfonyl mono- or dialkyl (C_{1-2}) -amino.

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2. A compound as claimed in claim 1, wherein A is CH_2 , Y is CH_2 , X is O, NH or NCH_3 , m and n are 0, and B has the meanings given in claim 1.

3. Pharmaceutical compositions containing at least one compound as claimed in 1 as an active component.

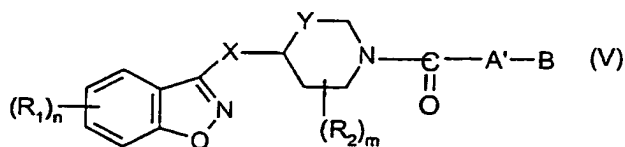
4. A method of preparing pharmaceutical compositions characterized in that a composition as claimed in 3 is prepared by bringing a compound as claimed in claim 1 in a form suitable for administration.
5. A method for the preparation of benzisoxazole derivatives, characterized in that a compound claimed in claim 1 is prepared by reaction of a compound of the formula (IV)



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a) with an optionally substituted 2- or 3-indolyl carboxylic acid derivative of the formula B-A'-COOH, wherein A' has the meaning (CRH)_p wherein R is hydrogen or methyl, and p is 0 or 1, followed by reduction of the keto group in the obtained compound of the formula (V):

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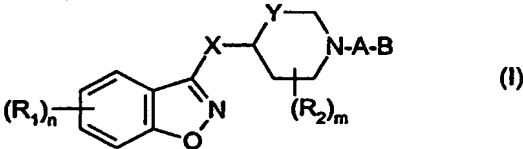


- or b) with an optionally substituted 2-halomethyl benzimidazole derivative of the formula B-A-Z, wherein B is the 2-benzimidazolyl group, A has the meaning given in claim 1, and Z is chloro or bromo.

6. A method of treating psychiatric disorders such as psychosis, anxiety, depression, attention deficits and memory disorders, neurological disorders such as Parkinson's disease and ischaemia and other CNS-diseases involving dopaminergic neurotransmission, characterized in that a compound as claimed in claim 1 is used.



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(54) Title: BENZISOXAZOLE DERIVATIVES HAVING D4-ANTAGONISTIC ACTIVITY <div style="text-align: center;">  (I) </div> (57) Abstract <p>The present invention relates to a group of novel benzisoxazole derivatives which are potent and selective antagonists of the dopamine D4-receptor. The compounds have general formula (I) wherein (R₁)_n represents 0, 1, or 2 substituents, which can be the same or different, from the group C₁₋₃-alkyl or alkoxy, halogen, trifluoromethyl, nitro, amino mono- or dialkyl (C₁₋₂)-amino, sulfonyl-(C₁₋₃)alkyl or -alkoxy, sulfonyl trifluoromethyl, sulfonyl amino, and sulfonyl mono- or dialkyl (C₁₋₂)-amino, X is O, S, NH or NCH₃, Y represents CH₂ or (CH₂)₂, (R₂)_m represents 0, 1, or 2 substituents, which can be the same or different, from the group methyl and ethyl, or (R₂)_m is a methylene bridge or ethylene bridge, A is a group -CH₂-(CRH)_p wherein R is hydrogen or methyl and p is 0 or 1, and B represents 2- or 3-indolyl or 2-benzimidazolyl, which groups may be substituted at carbon with 1 or 2 substituents from the group C₁₋₃-alkyl or alkoxy, halogen, trifluoromethyl, nitro, amino, mono- or dialkyl (C₁₋₂)amino, sulfonyl-(C₁₋₃)alkyl or -alkoxy, sulfonyl trifluoromethyl, sulfonyl amino, and sulfonyl mono- or dialkyl (C₁₋₂)-amino.</p>		

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CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

INTERNATIONAL SEARCH REPORT

International Application No

PC1/EP 99/00852

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D413/14 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4 352 811 A (J.T. STRUPCZEWSKI ET AL.) 5 October 1982 (1982-10-05) claims; examples 11-22,25,34 ---	1-6
Y	EP 0 602 242 A (YOSHITOMI PHARMACEUTICAL INDUSTRIES, LTD.) 22 June 1994 (1994-06-22) * claims, especially claims 7-9 and abstract * ---	1-6
A	EP 0 811 622 A (ADIR ET COMPAGNIE) 10 December 1997 (1997-12-10) claims ---	1-6
A	WO 94 27994 A (NOVO NORDISK A/S) 8 December 1994 (1994-12-08) claims --- -/--	1-6

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

5 October 1999

Date of mailing of the international search report

13/10/1999

Name and mailing address of the ISA

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Chouly, J

INTERNATIONAL SEARCH REPORT

Inter: *ional Application No

PC1/EP 99/00852

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	<p>WO 99 40067 A (TULP MARTINUS T M ;RONKEN ERIC (NL); DUPHAR INT RES (NL); VISSER G) 12 August 1999 (1999-08-12) the whole document -----</p>	1-6

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 99/ 00852

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 6
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 6
is directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims: it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/00852

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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WO 9940067	A	12-08-1999	NONE	

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Filed: December 23, 2002

Inventor: LEE, et. al.

Docket No. HMR2021 US ^{PCT} GNT

PRIOR ART